Management of Patients with Thyroid Carcinoma: Application of Thallium-201 Scintigraphy and Magnetic Resonance Imaging

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Thyroid carcinoma has the ability to concentrate radioiodine, an attribute that can be used both for detection of thyroid cells and for treatment. Unfortunately, however, radioiodine uptake is not observed in all patients and a radioiodine scan requires that the patient be rendered hypothyroid for 4–6 wk. In the present study, we analyzed the utility of thallium-201 scanning and the usefulness of magnetic resonance imaging (MRI) in the detection of thyroid cancer. Nineteen patients with thyroid cancer had a total of 24 radioiodine scans, 33 thallium scans, and 10 MRI examinations. Of the 19 patients in the study, 17 had differentiated thyroid carcinoma. In these 17 cases, all paired studies were concordant for the presence (n=7) or absence (n=10) of disease. However, in one case (Patient 10), the ^{201}Tl studies showed far more extensive disease than was observed on the ^{131}I scan. Thyroid cancer was also detected on seven MRI studies. In summary, thallium and MRI scans are adjunctive techniques to radioiodine scanning that can either confirm the presence of neck bed activity, residual disease or metastatic cancer and may delineate tumor deposits not detected by radioiodine scanning. Thallium may be capable of detecting tumor deposits even while a patient remains euthyroid.

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Thyroid carcinoma is a relatively common disorder that is unique among malignant neoplasms in that a specific radionuclide, iodine-131 (^{131}I), is effective in both detection and treatment of either residual thyroid bed or metastatic tumor (*1*). Ostensibly, it therefore would seem unnecessary to identify another radionuclide that might be useful in the detection and treatment of thyroid cancer. However, despite the utility of ^{131}I in these disorders, and the generally low morbidity and mortality rates for thyroid cancer, there are many individual patients who represent exceptions to these general observations. Differentiated thyroid cancer, particularly in older patients with pulmonary metastasis, can cause severe disability (*2*). Further, radioiodine uptake is not observed in a certain percentage of patients with differentiated thyroid cancer. Radioiodine scanning has the additional difficulty in that patients must discontinue thyroid medication for about 6-wk prior to effective scanning. The resulting hypothyroidism which develops may be discomforting to the patients. This inherent 6-wk delay before scanning may also allow the tumor to grow during the interim. Continued thyroid stimulating hormone (TSH) elevation during this prescanning period may act as a growth factor allowing the thyroid cancer to progress. This assumption underlies the practice of ensuring that, except during scanning periods, the serum TSH level should be suppressed in all thyroid patients for as long as possible. It is also well known that ^{131}I uptake is not demonstrated in other types of thyroid cancer, such as medullary and anaplastic; it would be very helpful if there were effective scanning agents for these tumors as well.

One agent that is useful in detecting thyroid cancers is thallium-201 (^{201}Tl) (*3–10*), which has been used extensively in clinical medicine for other indications (e.g., cardiac disease). Its specific advantages include being trapped mainly by heart and thyroid. It is a gamma emitter that can be detected by equipment commonly found in nuclear medicine clinics. The radionuclide is readily available and the scanning times are relatively short.

Thallium-201 has been reported to be an effective scanning agent in medullary thyroid cancer (*7*). Arnstein et al. (*7*) used this agent to localize residual medullary thyroid cancer in two patients who had previously had thyroidectomies, but continued to have elevated serum calcitonin levels. Talpos et al. (*8*) were able to localize residual medullary thyroid cancer in 5 of 10 patients with elevated serum calcitonin levels. Hoefnagel et al. (*11*) noted that 9 of 18 medullary

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TABLE 1
Thallium Thyroid Study

Patient	Date	Age	Sex	Diagnosis	^{131}I	^{201}Tl	TSH (μU/ml)	TG (ng/ml)	CT	MRI
1	08/30/88	31	F	P	NB 0.14%	N	84	<4	N/A	N/A
	11/02/88				N/A	P(focal area)	<0.15	<4	N/A	N/A
2	09/21/88	67	F	M Ca	N/A	N	53	—	Neg	Neg
	01/25/89				N/A	NB	1.1	<5	N/A	Neg*
3	12/12/88	39	F	F	NB 0.02%	N	17	<5	N/A	P
	03/15/89				NB 0.02%	—	96	12	N/A	N/A
4	02/27/89	50	F	P-F	N	N	89	<5	N/A	N/A
5	01/25/89	47	F	F	NB	N	<0.15	<4	N/A	N/A
	02/23/89				NB 0.17%	N	139	6	N/A	N/A
6	09/27/88	54	M	P-F	N/A	N	7	—	N/A	N/A
	12/13/88				NB	N	71	<5	N/A	N/A
7	08/26/88	46	M	P-F	NB 3.2%	NB	25	21	N/A	N/A
	10/20/88†				NB	P(SSN)	—	—	N/A	N/A
	02/07/89				NB	NB	3.4	10	N/A	N/A
8	02/06/89	74	F	F	P	P	0.32	0.15	N/A	N/A
9	01/13/89	58	M	P	N	N	146	<5	N/A	N/A
	11/01/88				N/A	N	<0.15	<5	N/A	N/A
10	10/14/88	53	F	F	P	P	138	103	P	Mets
11	02/03/89	38	F	P	NB	NB	0.15	34	N/A	P
	03/08/89				N/A	NB	56	Aby	N/A	N/A
12	11/18/88	55	M	P	N	N	—	17	N/A	Neg
13	10/28/88	44	F	P	N/A	N	0.15	<4	N/A	N/A
	12/02/88				N	N	69	<5	N/A	N/A
14	11/23/88	36	F	F	NB 0.1%	N	25	<5	N/A	N/A
15	01/31/89	32	F	P	N	N	150	<5	N/A	N/A
	12/12/88				N/A	N	<0.15	<5	N/A	N/A
16	12/14/88	50	M	P-F	N/A	P(axillary	<0.15	51	Neg	P
	02/09/89				PNeck	PNeck	<0.15	66	N/A	P
	05/14/89				Chest	Chest	4.1	276	N/A	P
17	04/14/89	31	F	P	NB	NB	89	8	N/A	N/A
18	06/14/88	81	F	P		NB	0.91	<4	P	P
	04/28/89			P	NB 0.23%	NB	<0.15	2	N/A	N/A
	07/17/89			P	NB 0.22%	NB	256	59	N/A	N/A
19	01/31/89	69	F	L	NB	N	115	11	N/A	N/A

* Basal calcitonin = 70 pg/ml.
Diagnosis: P = Papillary; F = Follicular; M Ca = Medullary Ca; P-F = papillary-follicular Ca; N = negative; P = positive; N/A = no scan; NB = neck bed activity only; SSN (Patient 7) = suprasternal notch; CT = CAT scan; MRI = magnetic resonance imaging; L = lymphoma of thyroid; and aby = antibody interference.
Normal ranges: TSH = 0.45–3.5 μU/ml; TG = less than 4 ng/ml in athyreotic patients.
Note: Dates given for scans and blood tests are approximate.
† T4 = 13.6 μg/dl.

thyroid cancers could be detected by ^{201}Tl studies, a finding consistent with that noted earlier. They also found that thallium scans may be helpful in detecting and localizing papillary and follicular thyroid cancer.

The purpose of our study is to extend these earlier reports by performing thallium scanning both in the euthyroid and hypothyroid states and to document that comparable scan results would be observed, thus confirming this utility of thallium for detecting residual tumor in patients who continue to take thyroid medication. Furthermore, we have compared, when possible, magnetic resonance scans and radioiodine scans in these same patients.

PATIENTS AND METHODS

Nineteen patients with thyroid cancer were studied. Eight patients had papillary, four had papillary-follicular, five had follicular, and one each had medullary thyroid cancer and lymphoma of the thyroid gland. Their average age was 50 yr and they had a total of 24 iodine scans, 33 thallium scans, and 10 MRIs of their neck or mediastinum. This study was approved by the hospital's clinical investigation committee and each patient gave informed consent. Whole-body scans were performed after administration of 2.0 mCi ^{201}Tl; both anterior and posterior images were obtained starting 15 min after injection. The gamma camera equipment used was a general-purpose parallel-hole collimator with an 80 and 167 keV window. The ^{131}I scans were performed 6 wk after the patient had discontinued thyroxine therapy and, in some cases, 3 wk after discontinuing T_3 therapy which had been given from 6 wk to 3 wk prior to scanning. Five millicuries of ^{131}I was administered and scans were performed 72 hr later; in some instances further scans were obtained between 72 and 96 hr after the dose. MRI scans were performed in 10 patients using standard T_1- and T_2-weighted spin-echo pulse sequences (1.5 T GE Signa Magnet, General Electric, Milwaukee, WI). Images were obtained in the axial and coronal planes. At the completion of the study, all nuclide studies weie reviewed by JA and all MRI studies were reviewed by JJ. These scans were again reviewed in a conference in which all scanning studies were reanalyzed and compared directly to one another. Lastly, the readings and analysis by the authors were compared to the original analysis of the scan at the time the study had been performed. Serum T_4 and T_3 were measured by specific automated coated tube radioimmunoassay (Micromedic Systems Inc., Horsham, PA) (*12*). TSH was measured by a highly sensitive assay in which the lower limit of detectability was 0.15 μU/ml and the normal range was 0.45-3.5 μU/ml (*13*) (Diagnostics Products Corp., Los Angeles, CA). Thyroglobulin was measured at Smith, Kline, and French laboratories by specific immunoassay (*14*).

RESULTS

Of the 19 patients in the study, 17 had differentiated thyroid carcinoma. In these 17 cases, all paired studies were concordant for the presence (n=7) or absence (n=10) of disease. However, in one case (Patient 10), the ^{201}Tl studies showed far more extensive disease than that observed on the ^{131}I scan. Three patients with papillary cancer did have apparent disease activity at the time of our study. Patient 16 (Figs. 1–3) was evaluated several times during his disease course. He had extensive local neck recurrence even though he had been treated with a total of ~800 mCi radioiodine (^{131}I). His radioiodine scan shows extensive activity in his neck, especially on the left, as well as evidence of pulmonary metastases; the thallium scan also demonstrated significant uptake in his left neck bed. Surprisingly, a computed tomography (CT) scan performed without contrast enhancement did not demonstrate definite evidence of disease activity, whereas the magnetic resonance imaging (MRI) studies distinctly demonstrated extensive left neck tumor, as well as tumor involvement of the left vocal cord, and the presence of a right supraclavicular node. Patient 18 (not shown) had a left neck mass detected, several years following surgery and radioiodine therapy, that was observed by ultrasound, CT, MRI, and radioiodine scanning. This suspected tumor mass has not been confirmed pathologically. Patient 7 (Fig. 4) seems to be free of disease

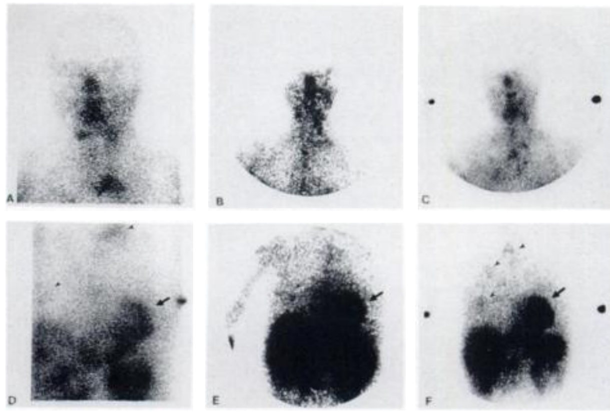

FIGURE 1
Patient 16. Thallium scans: upper row anterior head and neck, lower row anterior chest. A and D 12/14/88; B and E 2/9/89; C and F 5/14/89. All studies show multiple persistent areas of abnormal uptake in the neck, upper mediastinum, and left lower chest fields. These continue to visualize on the May 89 study while the T_4 was 15.7 μg/dl and the TSH 4.1 μU/ml. TG at this time was 276 ng/ml. Normal physiologic activity is seen in the heart (arrow), liver, and spleen. Arrowheads indicate tumor deposits.

activity, but did have a positive thallium scan in the left neck and supraclavicular area. Shortly after the scan, the patient was noted to have a stitch abscess that became clinically evident and was drained; the repeat

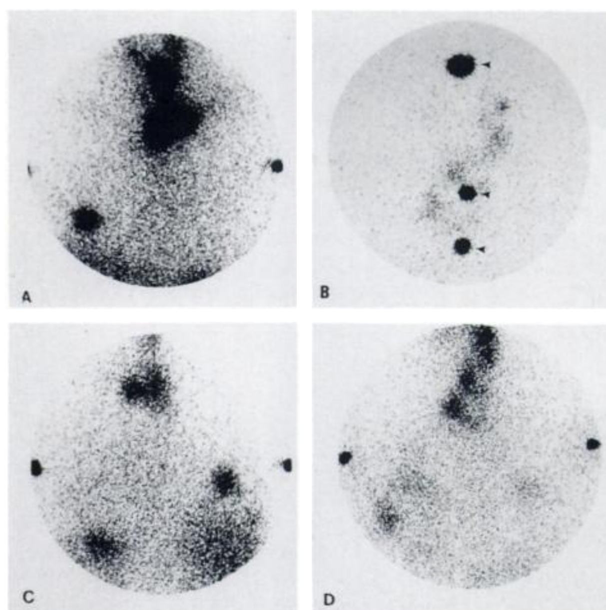

FIGURE 2
Patient 16. Iodine scans left column 3/15/88: (TSH > 50 μU/ml, TG = 51 ng/ml). (A) Anterior neck and (C) anterior chest. Right column 3/16/89: (TSH = 151 μU/ml, TG = 276 ng/ml). (B) pinhole neck with markers (arrow heads) on the thyroid cartilage and supra sternal notch and (D) anterior neck. The 1988 study shows area of abnormal uptake in the neck and right lower chest. The 1989 study shows persistent but diminished uptake in the neck and right lung field with new foci in the upper mediastinum.

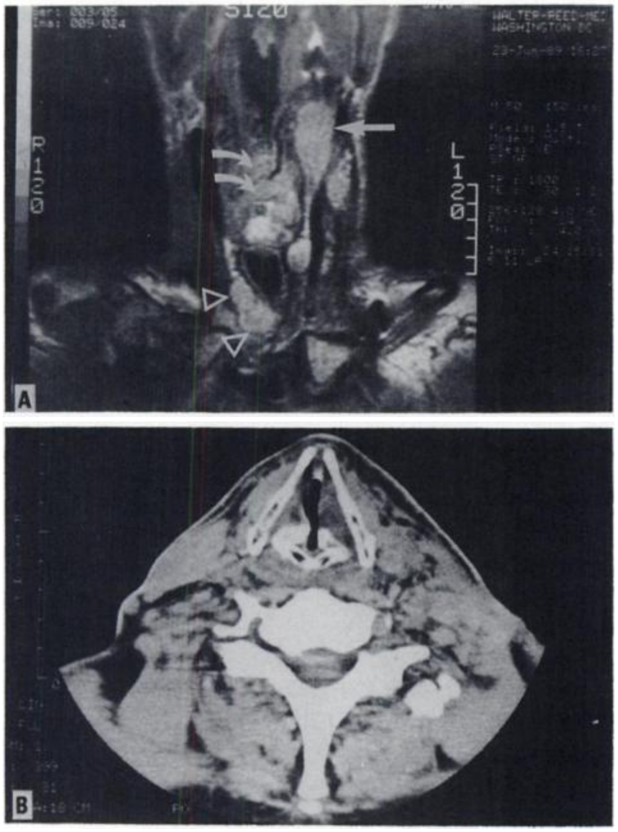

FIGURE 3
Patient 16. (A) Coronal proton-weighted magnetic resonance scan (TR-1800, TE-30) demonstrates recurrent tumor (straight arrow) with significant subglottic extension across the midline (curved arrows). A large right supraclavicular lymph node is present (arrowheads). (B) Axial CT through the level of the vocal cords shows assymetry of the right cord with irregular postoperative muscle planes on the left. A definite mass is not seen.

thallium study subsequently was devoid of activity in this area. Of the five patients with follicular cancer, three had extensive residual or recurrent disease. Patient 10 (Fig. 5) had extensive pulmonary metastases that were not distinctly and entirely detected by conventional radioiodine scans. Her thallium study, however, demonstrated significant and extensive disease in the pulmonary fields. This activity was also confirmed by both CT and MR studies (Fig. 6).

Furthermore, cytologic examination of her pulmonary effusion confirmed involvement by follicular thyroid cancer; the serum thyroglobulin level also was increased to 103 ng/ml. Patient 8 (Fig. 7) also had extensive disease in her lungs and skeleton that was confirmed by radioiodine and thallium scanning as well as by MRI. Patient 3 (not shown) participated in the study after a thyroidectomy and following surgical removal of metastases to her scapula and her cranium. When studied, her thallium and radioiodine scans were considered to be devoid of significant activity. Of interest, however, is the fact that when she presented with a

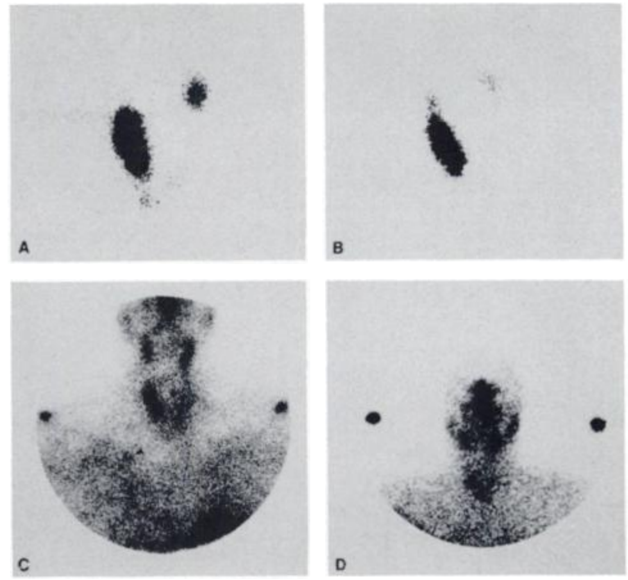

FIGURE 4
Patient 7. Top row: pinhole iodine neck scans. (A) 9/14/88 and (B) 3/17/89. Bottom row thallium anterior neck (C) 8/26/88 (T_4 = 3.8 μg/dl, TSH = 25 μU/ml, TG = 21 ng/ml) and (D) 2/7/89 (T_4 = 14.8 μg/dl, TSH = 3.4 μU/ml, TG = 10 ng/ml). Arrowhead in C denotes stitch abscess that was drained and then not noted on subsequent scan D. Persistent activity in area of thyroid bed is diminished on the 1989 studies.

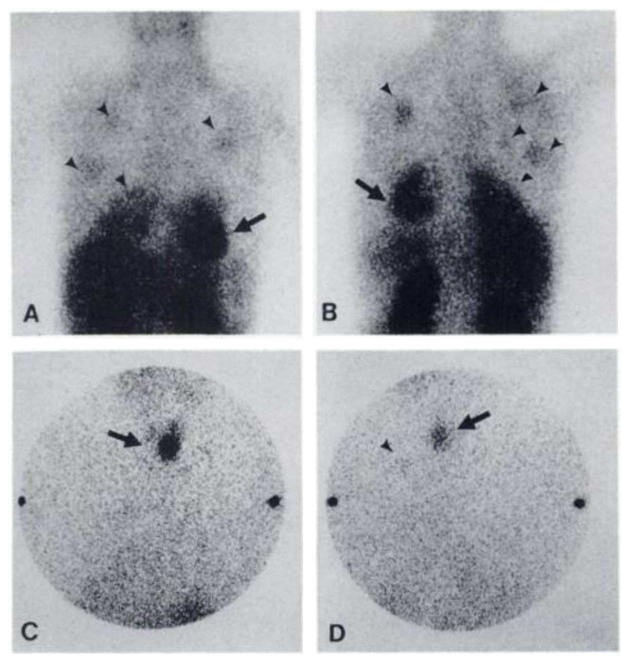

FIGURE 5
Patient 10. $T_4 < 1$ μg/dl, TSH = 138 μU/ml, TG = 103 ng/ml. Upper row thallium scan 10/14/88: (A) anterior chest and (B) posterior chest shows multiple areas (arrow heads) of abnormal uptake overyling the lung fields, but does not show any significant neck bed activity. Normal physiologic accumulation of thallium is seen in the heart (arrows) liver, spleen, and kidneys. Bottom row iodine scan 10/7/88. (C) Anterior chest and (D) posterior chest shows residual neck bed activity (arrows) but only faintly shows one lung lesion (arrow head) on the posterior.

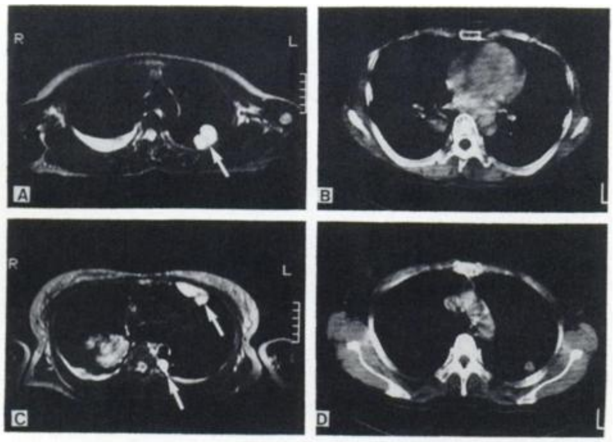

FIGURE 6
Patient 10. Left column (A and C): Axial magnetic resonance scan (2000, 80) shows a small right pleural effusion with parenchymal and pleural metastases (arrows). Right column (B and D): Axial CT of chest shows right hilar adenopathy as well as parenchymal metastases.

scapular mass, the source and type of tumor was unknown, and MRI of the scapula also was capable of detecting a well-defined, previously unsuspected right thyroid mass that was best seen in a T_2-weighted image. This thyroid mass was then operated upon and was found to be a clinically unsuspected and non-palpable thyroid follicular carcinoma.

The remaining two patients, one of whom had medullary thyroid cancer and the other thyroid lymphoma, had no significant disease detected by any scanning procedure, including ^{131}I-labeled metaiodobenzylguadine (MIBG) scanning of the patient with medullary carcinoma. Thyroid function tests were performed on all patients and confirmed that all patients having thyroid radioiodine scans were biochemically hypothyroid at that time. The sole exception was Patient 8 who had such significant follicular metastases that they functioned to render her only mildly biochemically hypothyroid (TSH = 15 μU/ml), despite the fact she had discontinued thyroid medication. Serum thyroglobulin levels also were performed and accurately assessed the presence of residual or extensive tumor.

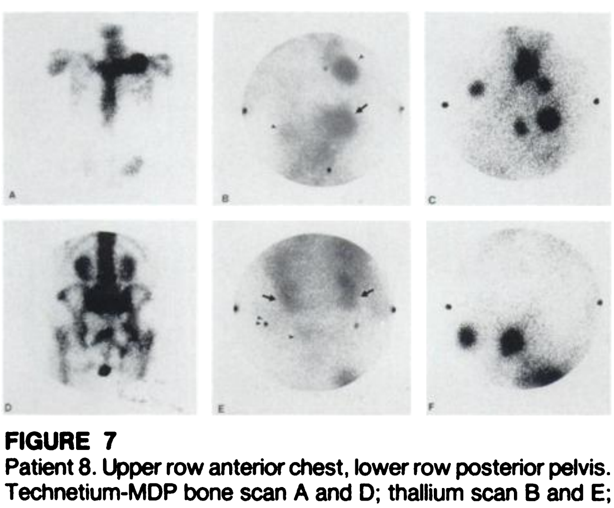

FIGURE 7
Patient 8. Upper row anterior chest, lower row posterior pelvis. Technetium-MDP bone scan A and D; thallium scan B and E; and iodine scan C and F (TSH = 15 μU/ml). All studies show lesions involving the left clavicle, left sacroiliac joint, left iliac crest, and right ischium. Normal physiologic activity is seen on the thallium scan in the heart and kidneys. (B) Arrow indicates normal heart activity. Arrowheads indicate tumor deposits. (E) Arrows indicate normal renal activity; arrowheads indicate tumor deposits.

DISCUSSION

In the present study, we used ^{201}Tl to detect residual or metastatic thyroid cancer and compared these results to conventional radioiodine scanning, and, when applicable, to magnetic resonance scanning. Our results demonstrate that ^{201}Tl scanning can detect residual or metastatic thyroid cancer and that such information can be used to direct further surgical or radiation therapy. Radioiodine scanning, of course, is the traditional method utilized to detect residual or metastatic thyroid tumor and our results in no way negate the utility of this important diagnostic and therapeutic agent. Nevertheless, we did find several patients (e.g., Patients 1, 10, and 16) whose tumors did not completely trap radioiodine well and, therefore, could not be detected by ^{131}I but were detectable by thallium scans, both in the neck bed and in metastatic locations. In other cases, both thallium and radioiodine scans had concordant results in that both were either positive for residual tissue or tumor or both showed no significant uptake. In our series, there were no cases in which radioiodine scanning detected tissue that could not be located by thallium scanning.

From these findings, we conclude that thallium scanning can be an effective means to detect residual thyroid tissue or metastatic disease. Thallium scanning has certain advantages over radioiodine; thallium scans can be performed even though the patient is continuing to take thyroid hormone medication. Indeed, for example, Patients 1, 7, and 16 each had positive thallium scans while they were euthyroid. This advantage has theoretical importance in patients with residual thyroid cancer since it may decrease the extent and duration of TSH-driven tumor stimulation. This advantage is also frequently useful in patients who are referred to our thyroid clinic from long distances and/or with a previous thyroidectomy of uncertain extent; thallium scans can be performed within the same day and will quickly provide added information. We do not interpret our data to suggest that thallium scanning should supplant standard methods of following patients with thyroid cancer, such as radioiodine scans and serum thyroglobulin levels (*2,14*). Rather, we view our data as indicating that in selected circumstances, such as negative iodine scan or patients referred from long distances while continuing to take thyroid medication, thallium scans can supplement information obtained by other techniques (*16*). Thallium scans, we believe, can also be useful in patients with known thyroid cancer and known residual or metastatic disease when intermittent thyroid medication is undesirable or not feasible. Of course, poorly differentiated thyroid cancers are unlikely to trap radioiodine, and thallium scanning might be particularly useful in these situations. Lymphoma of the thyroid may also be detected occasionally by thallium scanning, and MIBG may be useful in medullary thyroid cancer while no available scanning agent known seems useful in anaplastic carcinoma (*15*).

We have also found MRI to be extraordinarily useful in patients with residual or extensive thyroid carcinoma. MRI scans detected the sites and extent of tumor involvement quite well in several patients in particular (Patients 3, 10, 16, and 18). MRI scanning seems capable of detecting thyroid nodules, as well as metastatic or residual disease, and images these neoplasms better than CT in most cases (*17–21*). Additionally, CT of the neck is best evaluated following intravenous contrast which may be contraindicated in thyroid cancer patients because of the adverse effect of the iodine load upon ^{131}I uptake, imaging, and treatment. We do not believe that the MRI characteristics of a thyroid nodule can discern whether the tumor is benign or malignant. It does appear, however, that the strong signal intensity in a T_2-weighted image in patients with suspected metastatic thyroid cancer can help differentiate post-surgical changes or fibrosis from probable tumor on follow-up studies >6 mo from initial surgery (*20,22*).

We believe it is important to compare the advantages and disadvantages of thallium, radioiodine, and MRI scanning procedures in patients with suspected residual or metastatic thyroid cancer. The present study emphasizes the utility of each of these agents. Today, current clinical practice seems to depend solely on radioiodine scanning and serum thyroglobulin determinations. Our study clearly supports the utility of thallium and MRI scans in selected patients. Thallium is advantagous in that the scan can be performed while the patient continues to take thyroid medication, although further studies confirming this point are indicated. On the other hand, thallium may be concentrated by other disease processes, such as abscesses and other types of tumor, especially head and neck disease, and, thus, thallium must be considered to be less specific than radioactive iodine (*1,5*). In the clinical setting of patients with known thyroid cancer, this potential nonspecificity of thallium is less relevant. MRI scans are very effective in detecting residual or metastatic thyroid cancer and may even give some assessment of the extent of tumor or mass because of its ability to determine three-dimensional aspects. MRI scans, however, are expensive and some patients may exhibit claustrophobia, which may prevent them from having a scan performed.

There have been several studies published separately examining either thallium or MRI scans in patients with thyroid cancer (*1,9,11,18–24*). We believe the value of our study is that it compares thallium, radioactive iodine, and MRI scanning procedures in the same group of patients and, thus, allows direct analysis of the results. Previous studies examining thallium have also supported its efficacy as an adjunctive agent in thyroid cancer detection. MRI has not been extensively evaluated in this setting, as most of the earlier studies examined its utility in detecting thyroidal abnormalities rather than in assessing cancer recurrence. We conclude from our study that in selected patients both thallium and magnetic resonance scanning are quite helpful in assessing recurrent or residual disease and we shall now incorporate these clinical findings into our practice. We studied several patients who had disease detected, entirely or partially, by thallium scanning rather than by iodide scanning. These data support our view that thallium scanning may be useful especially in patients who are taking thyroid medication. Further comparative studies are indicated as are attempts to find newer scanning and therapeutic agents.

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Comprehensive Evaluation of Renal Function in the Transplanted Kidney

E.V. Dubovsky, J.R. Logic, A.G. Diethelm, C.M. Balch, and W.N. Tauxe

By means of a comprehensive renal function procedure (CRFP) based on the analysis of orthoiodohippurate kinetics carried out 223 times in 86 renal transplant patients, we have been able to separate clearly five clinical entities: normally functioning transplanted kidneys, acute tubular necrosis (ATN), cell-mediated rejection, humoral (chronic) rejection, and post-renal obstruction.

Forty-five studies were carried out in 22 living related donors. Five to seven days after surgery, the donor's effective renal plasma flow (ERPF) and excretory index (EI) were estimated and compared with preoperative values and with values of the recipient after transplantation.

A total of 223 CRFPs were carried out recently in 86 adult kidney recipients at the University of Alabama Medical Center. The protocol included three measurements of ERPF and EI during the first 24 hr after surgery, CRFP carried out postoperatively on Days 5, 12, and 19, and CRFP carried out 6-60 mo after transplantation. Patients were grouped as normally functioning (NF), acute or chronic rejection (AR, CR), ATN, and post-renal obstruction. The findings were then correlated with the clinical status of the patient, plasma creatinine, and blood urea nitrogen concentrations.

The CRFP consisted of several studies carried out concurrently, including: an angiographic perfusion study using 1 mCi of ^{99m}Tc-DTPA with the transplanted patient in the supine position and the scintillation camera detector positioned so that the bifurcation of the aorta, iliac arteries, and urinary bladder in addition to the kidney appeared in the camera field; and [^{131}I]OIH imaging precisely coordinated with blood and urine sampling.

The estimated mean ERPF utilizing these techniques equalled 337 $\pm$ 71 ml/min/1.73 m^2 in 96 determinations in normally functioning transplants. The ERPF of the single remaining kidney in a group of 15 donors 1 wk after surgery was 345 $\pm$ 68 ml/min/1.73 m^2. These values are not significantly different. Therefore, in the recipients, estimated ERPF values of 200-250 ml/min/1.73 m^2 were considered to represent the lower limits of normal, and values below 200 uniformly were regarded as abnormal.

This study suggests certain advantages of a combined and quantitative OIH excretion study in the evaluation of renal function and definition of several pathologic complications during the post-transplant period. The delayed cortical clearance of OIH and the associated decreased ERPF were found to antedate any biochemical or physiologic abnormality in impending acute rejection and may well represent a unique early sign of this complication. More recently, therapy has been started on patients with these findings. ■